

RESPIRATORY DISEASES AND IMMUNOCHEMISTRY

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Biologists, especially the geneticists, have long attempted by

chemical means to induce in higher organisms predictable and specific changes which thereafter could be transmitted in series as hereditary characters. Among microorganisms, the most striking and perhaps the only known example of inheritable and specific alterations in cell structure and function that can be experimentally induced and that are reproducible under well defined and adequately controlled conditions is the transformation of specific types of *Pneumococcus*. This phenomenon was first described by Griffith who succeeded in transforming an attenuated and non-encapsulated (R) variant derived from one specific type into fully encapsulated and virulent (S) cells of a heterologous specific type of *Pneumococcus*. A typical instance will suffice to illustrate the techniques originally used and serve to indicate the wide variety of transformations that are possible within the bacterial species. For example, Griffith found that mice injected subcutaneously with a small amount of a living R culture derived from *Pneumococcus* Type II together with a large inoculum of heat killed Type III (S) cells frequently succumbed to infection and that heart's blood of these animals yielded Type III pneumococci in pure culture. The fact that the R strain was avirulent and incapable by itself of causing fatal septicemia, and the additional fact that the heated suspension of Type III cells contained no viable organisms, brought convincing evidence that the R forms growing under these conditions had newly acquired the capsular structure and biological specificity of Type III pneumococci. Griffith wisely refrained from offering an explanation of the phenomenon beyond suggesting that the dead bacteria in the inoculum might furnish some specific protein that enables the R forms to manufacture a capsular carbohydrate of the same specific type as that of the S cells which serve as initial sources of the inducing substance.

Although the experiments in mice were successful, Griffith was unable to reproduce the phenomenon without mouse passage, and on the basis of negative results concluded that incubation of the bacterial mixture in vitro failed to induce transformation. These original observations were later confirmed by a number of people including workers in Dr. Avery's laboratory. Subsequently, it was shown by Dr. Dawson in Dr. Avery's laboratory that the transformation under certain conditions could be brought about in vitro. Further studies by Dr. MacLeod in Dr. Avery's laboratory threw light on many of the conditions necessary for the in vitro transformation.

For a number of years Dr. Avery and his associates have attempted to obtain in pure form the substance capable of bringing about this type of transformation in pneumococci. He believes that during the past year he has accomplished this. Without going into the technical details of how the material was obtained in a pure form, it can be stated that a substance, which according to chemical and physical criteria is relatively pure, has been obtained from pneumococci and that it will bring about the transformation spoken of above. This substance is desoxyribonucleic acid (thymus type).

The fact that the transforming substance in a purified state exhibits little or no immunological reactivity is in striking contrast to its biological function of inducing highly specific changes in living pneumococcal cells. As little as 0.02 μ g. representing a final dilution in the reacting system of 1:100,000,000 has sufficed to bring about the transformation of the R variant (R36A) into encapsulated Type III pneumococci. It is impossible as yet to appreciate the full importance of this work; in spite of that there is every reason to believe that it will have

a profound influence on the study of many problems in the biological field and that nucleic acids will assume new and broader significance.

In 1930 it was first recognized clearly that there exists a common clinical form of pneumonia which differs from the usual bacterial pneumonias. In the intervening years this illness, now termed "primary atypical pneumonia", has been encountered with increasing frequency. Interest in the condition stems from the facts that at the present time it is seen almost as frequently as is bacterial pneumonia and that the cause or causes of it have not been definitely established. There is reason to believe that this clinical syndrome is not a new disease. It was probably recognized occasionally during the second half of the last century and undoubtedly was observed not infrequently during each of the first three decades of this century. The recent marked increase in the use of the x-ray in acute respiratory diseases, the establishment of active full-time health units in some schools, colleges and camps, and the ineffectiveness of sulfonamide chemotherapy in the illness seem to have been the most important factors in bringing this syndrome into clear relief.

There can be no doubt that this condition, during the past three years, has been increasing in incidence more rapidly than can be accounted for on the basis merely of increased awareness and recognition of it by physicians. In certain Army camps in the continental United States the incidence of the illness has been as high as 1.3 per cent of the total command. It is recognized both by the Army and the Navy as responsible for more man-days lost from duty than almost any other acute infectious disease. The frequency with which the illness occurs among civilians cannot now be estimated due to the fact that, with the exception of New York City, the disease is not reportable.

Almost all investigators who have studied cases of primary atypical pneumonia think that the illness is not the result of bacterial infection. Some workers have suggested the possibility that the syndrome is caused by a virus and as a result the term "virus pneumonia" has come into common usage. There is evidence that the syndrome is not a single disease entity. Each of at least three different infectious agents has been shown to be etiologically related to certain small groups of cases. These are the psittacosis group of viruses, Rickettsia diaporica, and a virus infectious for the mongoose. Additional infectious agents have been suggested as possessing a causal relationship to other cases although the evidence upon which these suggestions have been based seems insufficient to permit of critical assessment.

A comprehensive study of primary atypical pneumonia was begun in the Rockefeller Hospital 18 months ago. The primary objectives of the study were two-fold: firstly, a detailed study of all the clinical manifestations of the illness; and secondly, an investigation of the nature of the infectious agents responsible for the syndrome. During this period 112 patients were admitted to the hospital with acute respiratory diseases. Of these, 80 were found to have primary atypical pneumonia. Specimens obtained from them constituted the source material for laboratory studies. In addition, specimens were also obtained from 211 patients with the disease in other civilian and military hospitals. All specimens have been stored at -70°C . and are constantly available for study. This large library of potentially infectious material has already proven of great value.

As a result of the detailed studies of 80 patients with primary atypical pneumonia, it has been possible to formulate a fairly accurate

clinical picture of the malady. It has also been possible to show that none of the usual pneumonia-producing bacteria and viruses was the cause of the disease in the patients studied. In addition, it was found that the sera of patients with the disease reacts in a peculiar manner in complement-fixation tests. This is an important observation because it invalidates certain conclusions based on the complement-fixation test arrived at by other workers. Finally, Dr. Horsfall and his associates have shown in a rather ingenious and indirect way that a virus is responsible for the malady in the patients studied. The workers accomplished this by injecting material from the patients into rabbits and showing that sera taken from such rabbits possess antibodies against a virus indigenous to white mice and etiologically unrelated to the pneumonia in human beings. Such a test reminds one of the Weil-Felix reaction in typhus fever. In this test, serum from convalescent typhus patients agglutinates proteus X19, a bacillus that has nothing to do with the causation of typhus fever.

Epidemic dysentery among members of the armed forces and civilian population is at present a problem of special concern to public health officials and to military authorities. Since the outbreak of the world conflict, clinical bacillary dysentery has been controlled largely through the use of sulfonamide drugs. The problem of procuring an efficacious prophylactic agent for the prevention of the disease among closely grouped peoples where the general sanitary conditions cannot be adequately controlled, has not been adequately solved. Dr. Goebel and his associates during the past year have attempted to isolate from certain types of Flexner dysentery bacilli, antigens which are relatively nontoxic and which will act as prophylactic vaccines in animals and human beings. Most of Dr. Goebel's work was conducted on the V strain of Flexner dysentery

bacilli because of the broad serological crossings which this strain exhibits with other members of the Flexner group. He has been able to isolate in several ways from these bacteria a carbohydrate-lipo-protein which when injected into rabbits and human beings leads to the production of antibodies that agglutinate dysentery bacilli. Further studies of this antigenic substance are under way and it is hoped that some kind of trial in the field may be carried out during the coming year.